DOCKET NO.: **2354/370**

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicant	:	Chai.	Examiner: Maher M Haddad
Serial No.	:	10/562,778	
Filed	:	June 30, 2004	Art Unit: 1644
Conf. No.	:		
For	:	METHODS AND COMPOSITIONS FOR TREATING DISORDERS OF THE EXTRACELLULAR MATRIX	

DECLARATION OF ZHONGLIN CHAI, PH.D., UNDER 37 C.F.R. §1.132

Mail Stop Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

I, Dr. Zonghlin Chai, pursuant to 37 C.F.R. § 1.132, hereby declare:

1. I trained in advanced virology and immunology in Nanjing Agricultural University (China), and subsequently completed a PhD in that field from Deakin University (Australia). in 1995.

2. I was the first person to identify and clone Cell Division Autoantigen 1 (CDA1) during my postdoctoral training in the Department of Pathology and Immunology, Monash University [J Biol Chem. 2001 Sep 7;276(36):33665-74]. My current research is focused on the biology of CDA1 and its roles in fibrosis, cell proliferation, and DNA damage response with the relevance of these actions to disorders such as diabetic complications and cancer.

3. I currently hold the position of Laboratory Head (Cell Proliferation and Fibrosis in Diabetic Complications Laboratory) in the Baker IDI Heart and Diabetes Institute. My team is investigating the basis of CDA1 action, and the relation of CDA1 to disease. My research activities also include active collaboration with other laboratories within the Baker IDI and

external collaborations including Prof Ban-Hock Toh's lab in Monash University (CDA1 in immunology), Prof Xinbin Chen from University of California, Davis (CDA1 in p53 regulation in DNA damage response) and Dr Hong-Jian Zhu from the University of Melbourne (CDA1 in TGF-β signaling).

4. The Australian patent attorneys for the Assignee (Dia-B Tech Limited) have explained to me that an adverse Office Action has issued in this case. The attorneys have shown me a copy of the Office Action, and have asked me to provide my opinion on various points raised by the Examiner.

5. I have reviewed the objection under numbered Paragraph 10 of the Office Action, and understand that the Examiner's objection relates to the enablement of claims directed to methods of treating or preventing diseases related to the aberrant synthesis of an ECM protein. The attorneys have informed me that in responding to the Office Action, the claims are to be restricted to methods for treating and preventing renal fibrosis caused by diabetes. I have therefore restricted my comments to the disease of diabetic renal fibrosis. The attorneys have also informed that the claims are to be limited to a method involving the modulation of CDA1. I further understand that the method will be restricted to the use of an AT1 receptor antagonist.

6. I understand from the Examiner's objection that a relevant question in the assessment of enablement is whether undue experimentation is required on the part of the skilled person to practice the invention across the scope of the claims. It is my opinion (and I believe others working in the field of researching and treating diabetic renal fibrosis) that the requirement to use "an AT1 receptor antagonist." is clear and provides sufficient direction to use one of a number of agents known at the priority date to have the recited activity.

7. Firstly, I note that the specification (on page 15, at line 12) provides Valsartan as one agent that could be used in the methods of treatment and prevention. Valsartan was known as an AT1 receptor antagonist at the priority date, being capable of binding and blocking the AT1 subtype of the angiotensin II receptor. At the priority date Valsartan was (and continues to be) a very widely prescribed drug and is marketed under a number trade names including DIOVAN™ (Novartis), VOLTAN™ (Cipa), and VALTAN™ (Torrent Pharmaceuticals). A

skilled person would have had no problem in obtaining this agent, and no reservations in administering it to a human subject given the previous use of the agent in hypertension. For example, DIOVAN™ has been registered for use in the United States since 1996, having had 7 years of post-marketing surveillance data at the priority date.

8. Valsartan (and other AT1 receptor antagonists) was indicated in the treatment of hypertension. It was known at the priority date that blockade of AT1 receptors directly causes vasodilation, reducing secretion of vasopressin, thereby reducing the production and secretion of aldosterone – the combined effect of which is reduction of blood pressure. To the best of my knowledge it was not known that Valsartan was capable of modulating the level of CDA1 in a kidney cell, thereby leading to a modulation in the production of extracellular matrix protein and a concomitant effect on the development or maintenance of fibrosis in the kidney.

9. If a clinician wished to treat a patient having diabetic renal fibrosis at the priority date using DIOVAN™, he or she would immediately understand that this condition is very different to the treatment of hypertension. However, the clinician would also understand that DIOVAN™ is nevertheless an AT1 receptor antagonist and would therefore be expected to be efficacious in diabetic renal fibrosis as proposed in the patent specification.

10. The first question that would occur to the clinician would be the correct dosage regime. A number of suitable regimes could be arrived at by reference to the "Full Prescribing Information" document as published by the manufacturer (Novartis). A copy of an exemplary document is attached herewith as Exhibit A.

11. The clinician would immediately refer to Section 2 of the exhibited document and note that for an adult patient, a dosage of 80 mg to 320 mg administered orally once per day is typically required. For a pediatric patient, a lower dosage of 1.3 mg/kg may be used as a starting dose. As for the vast majority of pharmaceutical agents, the clinician is not directed to a fixed dosage by the manufacturer but is instead provided with dosage ranges, and starting dosages. It is understood that dosages may need to be adjusted for each patient to obtain the required clinical effect while minimizing side effects. Such adjustments are routine in

clinical practice and are well within the skill of a physician or a scientist researching the effects of pharmaceutical agents.

12. It should be appreciated that the present invention is not limited solely to the use of Valsartan, and the skilled person would be familiar with a significant number of alternative AT1 receptor antagonists that were known at the priority date of this application. AT1 receptor antagonists were a recognized therapeutic class, with a number of agents being used clinically. AT1 receptor antagonists (other than Valsartan) known at the priority date including Candesartan (ATACAND™, BLOPRESS™, AMIAS™, RATACAND™, AstraZeneca and Takeda, Eprosartan (TEVETEN™, Abbott) , Irbesartan (APROVEL™, KARVEA™, AVAPRO™, Sanofi-Aventis, Bristol Myers Squibb) , Losartan (COZAAR™, Merck & Co.), Olmesartan (BENICAR™, OLMETEC™, Daichi Sankyo Ltd, Forrest Laboratories), Tasosartan (ANAZOR™) and Telmisartan (PRITOR™ or KINZAL™, Bayer Schering Pharma; MICARDIS, Boehringer Ingelheim; TELMA™, Glenmark Pharma, TELDAY™, Torrent Pharmaceuticals; and TELEACT D™, Ranbaxy. These agents are all used routinely in clinical practice and have demonstrated safety and efficacy as AT1 receptor antagonists. As mentioned above, none of these agents were indicated for the treatment of diabetic renal fibrosis before the priority date of this application.

13. In terms of dosage regimes, each of the agents recited at Paragraph 12 were marketed with prescribing information documents similar to that attached at Exhibit A. Accordingly, a physician or scientist would have had ample direction toward appropriate dosage regimes.

14. I further understand that under Paragraph 13 of the Office Action the Examiner has cited a prior art patent specification (United States Patent No. 6,211,217) relating to the use of Valsartan in the prevention of fibrosis occurring as a result of surgery. It was known at the priority date that fibrosis as a result of surgery is mechanistically far removed from that resulting from renal fibrosis caused by diabetes. Fibrosis caused by surgical trauma to a tissue triggers a strong and acute inflammatory response resulting in the influx of inflammatory cells to the site of injury. By contrast, diabetic renal fibrosis is not the result of tissue trauma, and does not result in the acute inflammatory responses seen in tissue injury. At the priority date, the mechanisms underlying diabetic renal fibrosis were not completely

understood, however increased pressure in the glomerulus of the kidneywas thought to be responsible to a large extent for fibrogenesis in the kidney of a diabetic patient.

15. Thus, the skilled person would not consider that any method useful for preventing fibrosis caused by surgical trauma, would be useful in the treatment of diabetic renal fibrosis. Given the knowledge at the priority date that these conditions are very likely mediated by separate mechanisms, there is nothing to suggest that use for diabetic renal fibrosis would be successful. While the Examiner has noted a reference to fibrosis of the kidney due to diabetes in the Background section of the 6,211,217, I would not take this as any suggestion to apply the methods disclosed in that patent to the treatment of diabetic renal fibrosis. The mention of kidney fibrosis was simply to explain that fibrosis in general is a significant clinical problem.

16. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Dated: 07 April 2009

Zhonglin Chai, Ph.D.

EXHIBIT A

Referred to in the Declaration of

ZHONGLIN CHAI

HIGHLIGHTS OF PRESCRIBING INFORMATION

These highlights do not include all the information needed to use Diovan safely and effectively. See full prescribing information for Diovan.

Diovan (valsartan) Tablets
Initial U.S. Approval: 1996

WARNING: USE IN PREGNANCY

When pregnancy is detected, discontinue Diovan as soon as possible. Drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus (5.1)

----------RECENT MAJOR CHANGES----------

None

----------INDICATIONS AND USAGE----------

Diovan is an angiotensin II receptor blocker (ARB) indicated for

- Treatment of hypertension (1.1)
- Treatment of heart failure (NYHA class II-IV). Diovan significantly reduced hospitalization for heart failure (1.2)
- Reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction (1.3)

----------DOSAGE AND ADMINISTRATION----------

Indication	Starting Dose	Dose Range	Target Maintenance Dose*
Adult Hypertension (2.1)	80 or 160 mg once daily	80-320 mg once daily	---
Pediatric Hypertension (6-16 years) (2.1)	1.3 mg/kg once daily (up to 40 mg total)	1.3-2.7 mg/kg once daily (up to 40-160 mg total)	---
Heart Failure (2.2)	40 mg twice daily	40-160 mg twice daily	160 mg twice daily
Post-Myocardial Infarction (2.3)	20 mg twice daily	20-160 mg twice daily	160 mg twice daily

* as tolerated by patient

No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver insufficiency. Care should be exercised with dosing of Diovan in patients with hepatic or severe renal impairment. Diovan may be administered with or without food. In heart failure patients, consideration should be given to reducing the dose of concomitant diuretics. Following myocardial infarction, consideration should be given to a dosage reduction if symptomatic hypotension or renal dysfunction occurs

----------DOSAGE FORMS AND STRENGTHS----------

Tablets (mg): 40 (scored), 80, 160, 320

----------CONTRAINDICATIONS----------

None

----------WARNINGS AND PRECAUTIONS----------

- Avoid fetal or neonatal exposure (5.1)
- Observe for signs and symptoms of hypotension (5.2)
- Use with caution in patients with impaired hepatic (5.3) or renal (5.4) function

----------ADVERSE REACTIONS----------

Hypertension: Most common adverse reactions are headache, dizziness, viral infection, fatigue and abdominal pain (6.1)
Heart Failure: Most common adverse reactions are dizziness, hypotension, diarrhea, arthralgia, back pain, fatigue and hyperkalemia (6.1)
Post-Myocardial Infarction: Most common adverse reactions which caused patients to discontinue therapy are hypotension, cough and increased blood creatinine (6.1)

To report SUSPECTED ADVERSE REACTIONS, contact Novartis Pharmaceuticals Corporation at 1-888-669-6682 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch

----------DRUG INTERACTIONS----------

Potassium sparing diuretics, potassium supplements or salt substitutes may lead to increases in serum potassium, and in heart failure patients, increases in serum creatinine (7)

----------USE IN SPECIFIC POPULATIONS----------

Nursing Mothers: Nursing or drug should be discontinued (8.3); **Pediatrics** Efficacy and safety data support use in 6-16 year old patients (8.4); **Geriatrics** No overall difference in efficacy or safety vs. younger patients, but greater sensitivity of some older individuals cannot be ruled out (8.5)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling

Revised: 12/2008

FULL PRESCRIBING INFORMATION: CONTENTS*

* Sections or subsections omitted from the full prescribing information are not listed

FULL PRESCRIBING INFORMATION

WARNING: USE IN PREGNANCY

When used in pregnancy, drugs that act directly on the renin-angiotensin system can cause injury and even death to the developing fetus. When pregnancy is detected, Diovan should be discontinued as soon as possible.

See **WARNINGS: Fetal/Neonatal Morbidity and Mortality (5.1)**

1 INDICATIONS AND USAGE

1.1 Hypertension

Diovan® (valsartan) is indicated for the treatment of hypertension. It may be used alone or in combination with other antihypertensive agents

1.2 Heart Failure

Diovan is indicated for the treatment of heart failure (NYHA class II-IV). In a controlled clinical trial, Diovan significantly reduced hospitalizations for heart failure. There is no evidence that Diovan provides added benefits when it is used with an adequate dose of an ACE inhibitor. *[See Clinical Studies (14.2)]*

1.3 Post-Myocardial Infarction

In clinically stable patients with left ventricular failure or left ventricular dysfunction following myocardial infarction, Diovan is indicated to reduce cardiovascular mortality. *[See Clinical Studies (14.3)]*

2 DOSAGE AND ADMINISTRATION

2.1 Adult Hypertension

The recommended starting dose of Diovan (valsartan) is 80 mg or 160 mg once daily when used as monotherapy in patients who are not volume-depleted. Patients requiring greater reductions may be started at the higher dose. Diovan may be used over a dose range of 80 mg to 320 mg daily, administered once a day.

The antihypertensive effect is substantially present within 2 weeks and maximal reduction is generally attained after 4 weeks. If additional antihypertensive effect is required over the starting dose range, the dose may be increased to a maximum of 320 mg or a diuretic may be added. Addition of a diuretic has a greater effect than dose increases beyond 80 mg.

No initial dosage adjustment is required for elderly patients, for patients with mild or moderate renal impairment, or for patients with mild or moderate liver insufficiency. Care should be exercised with dosing of Diovan in patients with hepatic or severe renal impairment.

Diovan may be administered with other antihypertensive agents.

Diovan may be administered with or without food.

2.2 Pediatric Hypertension 6-16 years of age

For children who can swallow tablets, the usual recommended starting dose is 1.3 mg/kg once daily (up to 40 mg total). The dosage should be adjusted according to blood pressure response. Doses higher than 2.7 mg/kg (up to 160 mg) once daily have not been studied in pediatric patients 6 to 16 years old.

For children who cannot swallow tablets, or children for whom the calculated dosage (mg/kg) does not correspond to the available tablet strengths of Diovan, the use of a suspension is recommended. Follow the suspension preparation instructions below (see **Preparation of Suspension**) to administer valsartan as a suspension. When the suspension is replaced by a tablet, the dose of valsartan may have to be increased. The exposure to valsartan with the suspension is 1.6 times greater than with the tablet.

Diovan is not recommended for treatment of children below the age of 6 years or children of any age with a glomerular filtration rate <30 mL/min/1.73 m^2, as no data are available

Preparation of Suspension (for 160 mL of a 4 mg/mL suspension)

Add 80 mL of Ora-Plus® oral suspending vehicle to an amber glass bottle containing 8 Diovan 80 mg tablets, and shake for a minimum of 2 minutes. Allow the suspension to stand for a minimum of 1 hour. After the standing time, shake the suspension for a minimum of 1 additional minute. Add 80 mL of Ora-Sweet SF® oral sweetening vehicle to the bottle and shake the suspension for at least 10 seconds to disperse the ingredients. The suspension is homogenous and can be

stored for either up to 30 days at room temperature (below 30°C/86°F) or up to 75 days at refrigerated conditions (2-8°C/35-46°F) in the glass bottle with a child-resistant screw-cap closure. Shake the bottle well (at least 10 seconds) prior to dispensing the suspension.

*Ora-Sweet SF® and Ora-Plus® are registered trademarks of Paddock Laboratories, Inc.

2.3 Heart Failure

The recommended starting dose of Diovan is 40 mg twice daily. Uptitration to 80 mg and 160 mg twice daily should be done to the highest dose, as tolerated by the patient. Consideration should be given to reducing the dose of concomitant diuretics. The maximum daily dose administered in clinical trials is 320 mg in divided doses.

2.4 Post-Myocardial Infarction

Diovan may be initiated as early as 12 hours after a myocardial infarction. The recommended starting dose of Diovan is 20 mg twice daily. Patients may be uptitrated within 7 days to 40 mg twice daily, with subsequent titrations to a target maintenance dose of 160 mg twice daily, as tolerated by the patient. If symptomatic hypotension or renal dysfunction occurs, consideration should be given to a dosage reduction. Diovan may be given with other standard post-myocardial infarction treatment, including thrombolytics, aspirin, beta-blockers, and statins.

3 DOSAGE FORMS AND STRENGTHS

40 mg are scored yellow ovaloid tablets with beveled edges, imprinted NVR/DO (Side 1/Side 2)

80 mg are pale red almond-shaped tablets with beveled edges, imprinted NVR/DV

160 mg are grey-orange almond-shaped tablets with beveled edges, imprinted NVR/DX

320 mg are dark grey-violet almond-shaped tablets with beveled edges, imprinted NVR/DXL

4 CONTRAINDICATIONS

None

5 WARNINGS AND PRECAUTIONS

5.1 Fetal/Neonatal Morbidity and Mortality

Diovan can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Drugs that act on the renin angiotensin system can cause fetal and neonatal morbidity and mortality when used in pregnancy. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. *[See Use in Specific Populations (8.1)]*

5.2 Hypotension

Excessive hypotension was rarely seen (0.1%) in patients with uncomplicated hypertension treated with Diovan alone. In patients with an activated renin-angiotensin system, such as volume- and/or salt-depleted patients receiving high doses of diuretics, symptomatic hypotension may occur. This condition should be corrected prior to administration of Diovan, or the treatment should start under close medical supervision.

Caution should be observed when initiating therapy in patients with heart failure or post-myocardial infarction patients. Patients with heart failure or post-myocardial infarction patients given Diovan commonly have some reduction in blood pressure, but discontinuation of therapy because of continuing symptomatic hypotension usually is not necessary when dosing instructions are followed. In controlled trials in heart failure patients, the incidence of hypotension in valsartan-treated patients was 5.5% compared to 1.8% in placebo-treated patients. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), hypotension in post-myocardial infarction patients led to permanent discontinuation of therapy in 1.4% of valsartan-treated patients and 0.8% of captopril-treated patients.

If excessive hypotension occurs, the patient should be placed in the supine position and, if necessary, given an intravenous infusion of normal saline. A transient hypotensive response is not a contraindication to further treatment, which usually can be continued without difficulty once the blood pressure has stabilized.

5.3 Impaired Hepatic Function

As the majority of valsartan is eliminated in the bile, patients with mild-to-moderate hepatic impairment, including patients with biliary obstructive disorders, showed lower valsartan clearance (higher AUCs). Care should be exercised in administering Diovan to these patients.

5.4 Impaired Renal Function

In studies of ACE inhibitors in hypertensive patients with unilateral or bilateral renal artery stenosis, increases in serum creatinine or blood urea nitrogen have been reported. In a 4-day trial of valsartan in 12 hypertensive patients with unilateral renal artery stenosis, no significant increases in serum creatinine or blood urea nitrogen were observed. There has been no long-term use of Diovan in patients with unilateral or bilateral renal artery stenosis, but an effect similar to that seen with ACE inhibitors should be anticipated.

As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function may be anticipated in susceptible individuals. In patients with severe heart failure whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, treatment with angiotensin-converting enzyme inhibitors and angiotensin receptor antagonists has been associated with oliguria and/or progressive azotemia and (rarely) with acute renal failure and/or death. Similar outcomes have been reported with Diovan.

Some patients with heart failure have developed increases in blood urea nitrogen, serum creatinine, and potassium. These effects are usually minor and transient, and they are more likely to occur in patients with pre-existing renal impairment. Dosage reduction and/or discontinuation of the diuretic and/or Diovan may be required. In the Valsartan Heart Failure Trial, in which 93% of patients were on concomitant ACE inhibitors, treatment was discontinued for elevations in creatinine or potassium (total of 1.0% on valsartan vs. 0.2% on placebo). In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), discontinuations due to various types of renal dysfunction occurred in 1.1% of valsartan-treated patients and 0.8% of captopril-treated patients. Evaluation of patients with heart failure or post-myocardial infarction should always include assessment of renal function.

6 ADVERSE REACTIONS

6.1 Clinical Studies Experience

Because clinical studies are conducted under widely varying conditions, adverse reactions rates observed in the clinical studies of a drug cannot be directly compared to rates in the clinical studies of another drug and may not reflect the rates observed in practice.

Adult Hypertension

Diovan (valsartan) has been evaluated for safety in more than 4,000 patients, including over 400 treated for over 6 months, and more than 160 for over 1 year. Adverse reactions have generally been mild and transient in nature and have only infrequently required discontinuation of therapy. The overall incidence of adverse reactions with Diovan was similar to placebo.

The overall frequency of adverse reactions was neither dose-related nor related to gender, age, race, or regimen. Discontinuation of therapy due to side effects was required in 2.3% of valsartan patients and 2.0% of placebo patients. The most common reasons for discontinuation of therapy with Diovan were headache and dizziness.

The adverse reactions that occurred in placebo-controlled clinical trials in at least 1% of patients treated with Diovan and at a higher incidence in valsartan (n=2,316) than placebo (n=888) patients included viral infection (3% vs. 2%), fatigue (2% vs. 1%), and abdominal pain (2% vs. 1%).

Headache, dizziness, upper respiratory infection, cough, diarrhea, rhinitis, sinusitis, nausea, pharyngitis, edema, and arthralgia occurred at a more than 1% rate but at about the same incidence in placebo and valsartan patients.

In trials in which valsartan was compared to an ACE inhibitor with or without placebo, the incidence of dry cough was significantly greater in the ACE-inhibitor group (7.9%) than in the groups who received valsartan (2.6%) or placebo (1.5%). In a 129-patient trial limited to patients who had had dry cough when they had previously received ACE inhibitors, the incidences of cough in patients who received valsartan, HCTZ, or lisinopril were 20%, 19%, and 69% respectively ($p < 0.001$).

Dose-related orthostatic effects were seen in less than 1% of patients. An increase in the incidence of dizziness was observed in patients treated with Diovan 320 mg (8%) compared to 10 to 160 mg (2% to 4%).

Diovan has been used concomitantly with hydrochlorothiazide without evidence of clinically important adverse interactions.

Other adverse reactions that occurred in controlled clinical trials of patients treated with Diovan (>0.2% of valsartan patients) are listed below. It cannot be determined whether these events were causally related to Diovan.

Body as a Whole: Allergic reaction and asthenia
Cardiovascular: Palpitations
Dermatologic: Pruritus and rash
Digestive: Constipation, dry mouth, dyspepsia, and flatulence
Musculoskeletal: Back pain, muscle cramps, and myalgia
Neurologic and Psychiatric: Anxiety, insomnia, paresthesia, and somnolence
Respiratory: Dyspnea
Special Senses: Vertigo
Urogenital: Impotence

Other reported events seen less frequently in clinical trials included chest pain, syncope, anorexia, vomiting, and angioedema.

Pediatric Hypertension

No relevant differences were identified between the adverse experience profile for pediatric patients aged 6-16 years and that previously reported for adult patients. Neurocognitive and developmental assessment of pediatric patients aged 6 to 16 years revealed no overall clinically relevant adverse impact after treatment with Diovan for up to one year.

In the one study (n=90) of pediatric patients (1-5 years), two deaths and three cases of on-treatment transaminase elevations were seen in the one-year open-label extension phase. These 5 events occurred in a study population in which patients frequently had significant co-morbidities. A causal relationship to Diovan has not been established.

Heart Failure

The adverse experience profile of Diovan in heart failure patients was consistent with the pharmacology of the drug and the health status of the patients. In the Valsartan Heart Failure Trial, comparing valsartan in total daily doses up to 320 mg (n=2,506) to placebo (n=2,494), 10% of valsartan patients discontinued for adverse reactions vs. 7% of placebo patients.

The table shows adverse reactions in double-blind short-term heart failure trials, including the first 4 months of the Valsartan Heart Failure Trial, with an incidence of at least 2% that were more frequent in valsartan-treated patients than in placebo-treated patients. All patients received standard drug therapy for heart failure, frequently as multiple medications, which could include diuretics, digitalis, beta-blockers, or ACE inhibitors.

	Valsartan (n=3,282)	Placebo (n=2,740)
Dizziness	17%	9%
Hypotension	7%	2%
Diarrhea	5%	4%
Arthralgia	3%	2%
Fatigue	3%	2%
Back Pain	3%	2%
Dizziness, postural	2%	1%
Hyperkalemia	2%	1%
Hypotension, postural	2%	1%

Other adverse reactions with an incidence greater than 1% and greater than placebo included headache NOS, nausea, renal impairment NOS, syncope, blurred vision, upper abdominal pain and vertigo. (NOS = not otherwise specified).

From the long-term data in the Valsartan Heart Failure Trial, there did not appear to be any significant adverse reactions not previously identified.

Post-Myocardial Infarction

The safety profile of Diovan was consistent with the pharmacology of the drug and the background diseases, cardiovascular risk factors, and clinical course of patients treated in the post-myocardial infarction setting. The table

shows the percent of patients discontinued in the valsartan and captopril-treated groups in the Valsartan in Acute Myocardial Infarction Trial (VALIANT) with a rate of at least 0.5% in either of the treatment groups.

	Valsartan (n=4,885)	Captopril (n=4,879)
Discontinuation for adverse reaction	5.8%	7.7%
Adverse reactions		
Hypotension NOS	1.4%	0.8%
Cough	0.6%	2.5%
Blood creatinine increased	0.6%	0.4%
Rash NOS	0.2%	0.6%

6.2 Post-Marketing Experience

The following additional adverse reactions have been reported in post-marketing experience:

Hypersensitivity: There are rare reports of angioedema;
Digestive: Elevated liver enzymes and very rare reports of hepatitis;
Renal: Impaired renal function;
Clinical Laboratory Tests: Hyperkalemia;
Dermatologic: Alopecia.
Blood and Lymphatic: There are very rare reports of thrombocytopenia.
Vascular: Vasculitis.

Rare cases of rhabdomyolysis have been reported in patients receiving angiotensin II receptor blockers.

Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

7 DRUG INTERACTIONS

No clinically significant pharmacokinetic interactions were observed when Diovan (valsartan) was coadministered with amlodipine, atenolol, cimetidine, digoxin, furosemide, glyburide, hydrochlorothiazide, or indomethacin. The valsartan-atenolol combination was more antihypertensive than either component, but it did not lower the heart rate more than atenolol alone.

Coadministration of valsartan and warfarin did not change the pharmacokinetics of valsartan or the time-course of the anticoagulant properties of warfarin.

CYP 450 Interactions: The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes. The inhibitory or induction potential of valsartan on CYP 450 is also unknown.

Transporters: The results from an *in vitro* study with human liver tissue indicate that valsartan is a substrate of the hepatic uptake transporter OATP1B1 and the hepatic efflux transporter MRP2. Co-administration of inhibitors of the uptake transporter (rifampin, cyclosporine) or efflux transporter (ritonavir) may increase the systemic exposure to valsartan.

As with other drugs that block angiotensin II or its effects, concomitant use of potassium sparing diuretics (e.g. spironolactone, triamterene, amiloride), potassium supplements, or salt substitutes containing potassium may lead to increases in serum potassium and in heart failure patients to increases in serum creatinine.

7.1 Clinical Laboratory Test Findings

In controlled clinical trials, clinically important changes in standard laboratory parameters were rarely associated with administration of Diovan.

Creatinine: Minor elevations in creatinine occurred in 0.8% of patients taking Diovan and 0.6% given placebo in controlled clinical trials of hypertensive patients. In heart failure trials, greater than 50% increases in creatinine were observed in 3.9% of Diovan-treated patients compared to 0.9% of placebo-treated patients. In post-myocardial infarction patients, doubling of serum creatinine was observed in 4.2% of valsartan-treated patients and 3.4% of captopril-treated patients.

Hemoglobin and Hematocrit: Greater than 20% decreases in hemoglobin and hematocrit were observed in 0.4% and 0.8%, respectively, of Diovan patients, compared with 0.1% and 0.1% in placebo-treated patients. One valsartan patient discontinued treatment for microcytic anemia.

Liver Function Tests: Occasional elevations (greater than 150%) of liver chemistries occurred in Diovan-treated patients. Three patients (< 0.1%) treated with valsartan discontinued treatment for elevated liver chemistries.

Neutropenia: Neutropenia was observed in 1.9% of patients treated with Diovan and 0.8% of patients treated with placebo.

Serum Potassium: In hypertensive patients, greater than 20% increases in serum potassium were observed in 4.4% of Diovan-treated patients compared to 2.9% of placebo-treated patients. In heart failure patients, greater than 20% increases in serum potassium were observed in 10.0% of Diovan-treated patients compared to 5.1% of placebo-treated patients.

Blood Urea Nitrogen (BUN): In heart failure trials, greater than 50% increases in BUN were observed in 16.6% of Diovan-treated patients compared to 6.3% of placebo-treated patients.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy

Teratogenic Effects: Pregnancy Category D

Diovan, like other drugs that act on the renin angiotensin system, can cause fetal and neonatal morbidity and death when used during the second or third trimester of pregnancy. Diovan can cause fetal harm when administered to a pregnant woman. If this drug is used during pregnancy, or if the patient becomes pregnant while taking this drug, the patient should be apprised of the potential hazard to the fetus.

Angiotensin II receptor antagonists, like valsartan, and angiotensin converting enzyme (ACE) inhibitors exert similar effects on the renin-angiotensin system. In several dozen published cases, ACE inhibitor use during the second and third trimesters of pregnancy was associated with fetal and neonatal injury, including hypotension, neonatal skull hypoplasia, anuria, reversible or irreversible renal failure, and death. Oligohydramnios was also reported, presumably from decreased fetal renal function. In this setting, oligohydramnios was associated with fetal limb contractures, craniofacial deformation, and hypoplastic lung development. Prematurity, intrauterine growth retardation, and patent ductus arteriosus were also reported, although it is not clear whether these occurrences were due to exposure to the drug. In a retrospective study, first trimester use of ACE inhibitors, a specific class of drugs acting on the renin angiotensin system, was associated with a potential risk of birth defects.

When pregnancy occurs in a patient using Diovan, the physician should discontinue Diovan treatment as soon as possible. The physician should inform the patient about potential risks to the fetus based on the time of gestational exposure to Diovan (first trimester only or later). If exposure occurs beyond the first trimester, an ultrasound examination should be done.

In rare cases when another antihypertensive agent can not be used to treat the pregnant patient, serial ultrasound examinations should be performed to assess the intraamniotic environment. Routine fetal testing with non-stress tests, biophysical profiles, and/or contraction stress tests may be appropriate based on gestational age and standards of care in the community. If oligohydramnios occurs in these situations, individualized decisions about continuing or discontinuing Diovan treatment and about pregnancy management should be made by the patient, her physician, and experts in the management of high risk pregnancy. Patients and physicians should be aware that oligohydramnios may not appear until after the fetus has sustained irreversible injury.

Infants with histories of in utero exposure to Diovan should be closely observed for hypotension, oliguria, and hyperkalemia. If oliguria occurs, these infants may require blood pressure and renal perfusion support. Exchange transfusion or dialysis may be required to reverse hypotension and/or support decreased renal function.

Healthcare professionals who prescribe drugs acting directly on the renin angiotensin system should counsel women of childbearing potential about the risks of these agents during pregnancy. *[See Nonclincial Toxicology (13.2)]*

8.3 Nursing Mothers

It is not known whether Diovan is excreted in human milk. Diovan was excreted in the milk of lactating rats; however, animal breast milk drug levels may not accurately reflect human breast milk levels. Because many drugs are excreted into human milk and because of the potential for adverse reactions in nursing infants from Diovan, a decision should be made whether to discontinue nursing or discontinue the drug, taking into account the importance of the drug to the mother.

8.4 Pediatric Use

The antihypertensive effects of Diovan have been evaluated in two randomized, double-blind clinical studies in pediatric patients from 1-5 and 6-16 years of age *[see Clinical Studies(14.1)]*. The pharmacokinetics of Diovan have been evaluated

in pediatric patients 1 to 16 years of age *[see Pharmacokinetics, Special Populations, Pediatric (12.3)]*. Diovan was generally well tolerated in children 6-16 years and the adverse experience profile was similar to that described for adults. Diovan is not recommended for pediatric patients under 6 years of age due to safety findings for which a relationship to treatment could not be excluded *[see Adverse Reactions, Pediatric Hypertension (6.1)]*.

Daily oral dosing of neonatal/juvenile rats with valsartan at doses as low as 1 mg/kg/day (about 10% of the maximum recommended pediatric dose on a mg/m^2 basis) from postnatal day 7 to postnatal day 70 produced persistent, irreversible kidney damage. These kidney effects in neonatal rats represent expected exaggerated pharmacological effects that are observed if rats are treated during the first 13 days of life. Since this period coincides with up to 44 weeks after conception in humans, it is not considered to point toward an increased safety concern in 6 to 16 year old children.

Diovan is not recommended for treatment of children with glomerular filtration rates <30 mL/min/1.73 m^2, as no data are available.

8.5 Geriatric Use

In the controlled clinical trials of valsartan, 1,214 (36.2%) of hypertensive patients treated with valsartan were ≥65 years and 265 (7.9%) were ≥75 years. No overall difference in the efficacy or safety of valsartan was observed in this patient population, but greater sensitivity of some older individuals cannot be ruled out.

Of the 2,511 patients with heart failure randomized to valsartan in the Valsartan Heart Failure Trial, 45% (1,141) were 65 years of age or older. In the Valsartan in Acute Myocardial Infarction Trial (VALIANT), 53% (2,596) of the 4,909 patients treated with valsartan and 51% (2,515) of the 4,885 patients treated with valsartan + captopril were 65 years of age or older. There were no notable differences in efficacy or safety between older and younger patients in either trial.

10 OVERDOSAGE

Limited data are available related to overdosage in humans. The most likely manifestations of overdosage would be hypotension and tachycardia; bradycardia could occur from parasympathetic (vagal) stimulation. Depressed level of consciousness, circulatory collapse and shock have been reported. If symptomatic hypotension should occur, supportive treatment should be instituted.

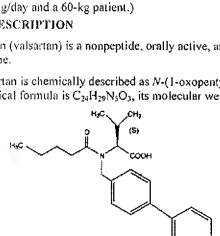
Diovan (valsartan) is not removed from the plasma by hemodialysis.

Valsartan was without grossly observable adverse effects at single oral doses up to 2000 mg/kg in rats and up to 1000 mg/kg in marmosets, except for salivation and diarrhea in the rat and vomiting in the marmoset at the highest dose (60 and 31 times, respectively, the maximum recommended human dose on a mg/m^2 basis). (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

11 DESCRIPTION

Diovan (valsartan) is a nonpeptide, orally active, and specific angiotensin II receptor blocker acting on the AT_1 receptor subtype.

Valsartan is chemically described as *N*-(1-oxopentyl)-*N*-[[2′-(1*H*-tetrazol-5-yl) [1,1′-biphenyl]-4-yl]methyl]-L-valine. Its empirical formula is $C_{24}H_{29}N_5O_3$, its molecular weight is 435.5, and its structural formula is



Valsartan is a white to practically white fine powder. It is soluble in ethanol and methanol and slightly soluble in water.

Diovan is available as tablets for oral administration, containing 40 mg, 80 mg, 160 mg or 320 mg of valsartan. The inactive ingredients of the tablets are colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides

(yellow, black and/or red), magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide.

12 CLINICAL PHARMACOLOGY

12.1 Mechanism of Action

Angiotensin II is formed from angiotensin I in a reaction catalyzed by angiotensin-converting enzyme (ACE, kininase II). Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation, and renal reabsorption of sodium. Diovan (valsartan) blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT_1 receptor in many tissues, such as vascular smooth muscle and the adrenal gland. Its action is therefore independent of the pathways for angiotensin II synthesis.

There is also an AT_2 receptor found in many tissues, but AT_2 is not known to be associated with cardiovascular homeostasis. Valsartan has much greater affinity (about 20,000-fold) for the AT_1 receptor than for the AT_2 receptor. The increased plasma levels of angiotensin II following AT_1 receptor blockade with valsartan may stimulate the unblocked AT_2 receptor. The primary metabolite of valsartan is essentially inactive with an affinity for the AT_1 receptor about one-200th that of valsartan itself.

Blockade of the renin-angiotensin system with ACE inhibitors, which inhibit the biosynthesis of angiotensin II from angiotensin I, is widely used in the treatment of hypertension. ACE inhibitors also inhibit the degradation of bradykinin, a reaction also catalyzed by ACE. Because valsartan does not inhibit ACE (kininase II), it does not affect the response to bradykinin. Whether this difference has clinical relevance is not yet known. Valsartan does not bind to or block other hormone receptors or ion channels known to be important in cardiovascular regulation.

Blockade of the angiotensin II receptor inhibits the negative regulatory feedback of angiotensin II on renin secretion, but the resulting increased plasma renin activity and angiotensin II circulating levels do not overcome the effect of valsartan on blood pressure.

12.2 Pharmacodynamics

Valsartan inhibits the pressor effect of angiotensin II infusions. An oral dose of 80 mg inhibits the pressor effect by about 80% at peak with approximately 30% inhibition persisting for 24 hours. No information on the effect of larger doses is available.

Removal of the negative feedback of angiotensin II causes a 2- to 3-fold rise in plasma renin and consequent rise in angiotensin II plasma concentration in hypertensive patients. Minimal decreases in plasma aldosterone were observed after administration of valsartan; very little effect on serum potassium was observed.

In multiple-dose studies in hypertensive patients with stable renal insufficiency and patients with renovascular hypertension, valsartan had no clinically significant effects on glomerular filtration rate, filtration fraction, creatinine clearance, or renal plasma flow.

In multiple-dose studies in hypertensive patients, valsartan had no notable effects on total cholesterol, fasting triglycerides, fasting serum glucose, or uric acid.

12.3 Pharmacokinetics

Valsartan peak plasma concentration is reached 2 to 4 hours after dosing. Valsartan shows bi-exponential decay kinetics following intravenous administration, with an average elimination half-life of about 6 hours. Absolute bioavailability for Diovan is about 25% (range 10%-35%). The bioavailability of the suspension (see [2.2] Dosage and Administration; Pediatric Hypertension) is 1.6 times greater than with the tablet. With the tablet, food decreases the exposure (as measured by AUC) to valsartan by about 40% and peak plasma concentration (C_{max}) by about 50%. AUC and C_{max} values of valsartan increase approximately linearly with increasing dose over the clinical dosing range. Valsartan does not accumulate appreciably in plasma following repeated administration.

Metabolism and Elimination: Valsartan, when administered as an oral solution, is primarily recovered in feces (about 83% of dose) and urine (about 13% of dose). The recovery is mainly as unchanged drug, with only about 20% of dose recovered as metabolites. The primary metabolite, accounting for about 9% of dose, is valeryl 4-hydroxy valsartan. The enzyme(s) responsible for valsartan metabolism have not been identified but do not seem to be CYP 450 isozymes.

Following intravenous administration, plasma clearance of valsartan is about 2 L/h and its renal clearance is 0.62 L/h (about 30% of total clearance).

Distribution: The steady state volume of distribution of valsartan after intravenous administration is small (17 L), indicating that valsartan does not distribute into tissues extensively. Valsartan is highly bound to serum proteins (95%), mainly serum albumin.

Special Populations:

Pediatric: In a study of pediatric hypertensive patients (n=26, 1-16 years of age) given single doses of a suspension of Diovan (mean: 0.9 to 2 mg/kg), the clearance (L/h/kg) of valsartan for children was similar to that of adults receiving the same formulation.

Geriatric: Exposure (measured by AUC) to valsartan is higher by 70% and the half-life is longer by 35% in the elderly than in the young. No dosage adjustment is necessary *[see Dosage and Administration (2.1)]*.

Gender: Pharmacokinetics of valsartan does not differ significantly between males and females.

Heart Failure: The average time to peak concentration and elimination half-life of valsartan in heart failure patients are similar to that observed in healthy volunteers. AUC and C_{max} values of valsartan increase linearly and are almost proportional with increasing dose over the clinical dosing range (40 to 160 mg twice a day). The average accumulation factor is about 1.7. The apparent clearance of valsartan following oral administration is approximately 4.5 L/h. Age does not affect the apparent clearance in heart failure patients.

Renal Insufficiency: There is no apparent correlation between renal function (measured by creatinine clearance) and exposure (measured by AUC) to valsartan in patients with different degrees of renal impairment. Consequently, dose adjustment is not required in patients with mild-to-moderate renal dysfunction. No studies have been performed in patients with severe impairment of renal function (creatinine clearance <10 mL/min). Valsartan is not removed from the plasma by hemodialysis. In the case of severe renal disease, exercise care with dosing of valsartan *[see Dosage and Administration (2.1)]*.

Hepatic Insufficiency: On average, patients with mild-to-moderate chronic liver disease have twice the exposure (measured by AUC values) to valsartan of healthy volunteers (matched by age, sex and weight). In general, no dosage adjustment is needed in patients with mild-to-moderate liver disease. Care should be exercised in patients with liver disease *[see Dosage and Administration (2.1)]*.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility

There was no evidence of carcinogenicity when valsartan was administered in the diet to mice and rats for up to 2 years at doses up to 160 and 200 mg/kg/day, respectively. These doses in mice and rats are about 2.6 and 6 times, respectively, the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

Mutagenicity assays did not reveal any valsartan-related effects at either the gene or chromosome level. These assays included bacterial mutagenicity tests with *Salmonella* (Ames) and *E coli*; a gene mutation test with Chinese hamster V79 cells; a cytogenetic test with Chinese hamster ovary cells; and a rat micronucleus test.

Valsartan had no adverse effects on the reproductive performance of male or female rats at oral doses up to 200 mg/kg/day. This dose is 6 times the maximum recommended human dose on a mg/m^2 basis. (Calculations assume an oral dose of 320 mg/day and a 60-kg patient.)

13.2 Animal Toxicology and/or Pharmacology

Reproductive Toxicology Studies

No teratogenic effects were observed when valsartan was administered to pregnant mice and rats at oral doses up to 600 mg/kg/day and to pregnant rabbits at oral doses up to 10 mg/kg/day. However, significant decreases in fetal weight, pup birth weight, pup survival rate, and slight delays in developmental milestones were observed in studies in which parental rats were treated with valsartan at oral, maternally toxic (reduction in body weight gain and food consumption) doses of 600 mg/kg/day during organogenesis or late gestation and lactation. In rabbits, fetotoxicity (i.e., resorptions, litter loss, abortions, and low body weight) associated with maternal toxicity (mortality) was observed at doses of 5 and 10 mg/kg/day. The no observed adverse effect doses of 600, 200 and 2 mg/kg/day in mice, rats and rabbits represent 9, 6, and 0.1 times, respectively, the maximum recommended human dose on a mg/m^2 basis. Calculations assume an oral dose of 320 mg/day and a 60-kg patient.

14 CLINICAL STUDIES

14.1 Hypertension

Adult Hypertension

The antihypertensive effects of Diovan (valsartan) were demonstrated principally in 7 placebo-controlled, 4- to 12-week trials (one in patients over 65) of dosages from 10 to 320 mg/day in patients with baseline diastolic blood pressures of 95-115. The studies allowed comparison of once-daily and twice-daily regimens of 160 mg/day; comparison of peak and trough effects; comparison (in pooled data) of response by gender, age, and race; and evaluation of incremental effects of hydrochlorothiazide.

Administration of valsartan to patients with essential hypertension results in a significant reduction of sitting, supine, and standing systolic and diastolic blood pressure, usually with little or no orthostatic change.

In most patients, after administration of a single oral dose, onset of antihypertensive activity occurs at approximately 2 hours, and maximum reduction of blood pressure is achieved within 6 hours. The antihypertensive effect persists for 24 hours after dosing, but there is a decrease from peak effect at lower doses (40 mg) presumably reflecting loss of inhibition of angiotensin II. At higher doses, however (160 mg), there is little difference in peak and trough effect. During repeated dosing, the reduction in blood pressure with any dose is substantially present within 2 weeks, and maximal reduction is generally attained after 4 weeks. In long-term follow-up studies (without placebo control), the effect of valsartan appeared to be maintained for up to two years. The antihypertensive effect is independent of age, gender or race. The latter finding regarding race is based on pooled data and should be viewed with caution, because antihypertensive drugs that affect the renin-angiotensin system (that is, ACE inhibitors and angiotensin-II blockers) have generally been found to be less effective in low-renin hypertensives (frequently blacks) than in high-renin hypertensives (frequently whites). In pooled, randomized, controlled trials of Diovan that included a total of 140 blacks and 830 whites, valsartan and an ACE-inhibitor control were generally at least as effective in blacks as whites. The explanation for this difference from previous findings is unclear.

Abrupt withdrawal of valsartan has not been associated with a rapid increase in blood pressure.

The blood pressure lowering effect of valsartan and thiazide-type diuretics are approximately additive.

The 7 studies of valsartan monotherapy included over 2,000 patients randomized to various doses of valsartan and about 800 patients randomized to placebo. Doses below 80 mg were not consistently distinguished from those of placebo at trough, but doses of 80, 160 and 320 mg produced dose-related decreases in systolic and diastolic blood pressure, with the difference from placebo of approximately 6-9/3-5 mmHg at 80-160 mg and 9/6 mmHg at 320 mg. In a controlled trial the addition of HCTZ to valsartan 80 mg resulted in additional lowering of systolic and diastolic blood pressure by approximately 6/3 and 12/5 mmHg for 12.5 and 25 mg of HCTZ, respectively, compared to valsartan 80 mg alone.

Patients with an inadequate response to 80 mg once daily were titrated to either 160 mg once daily or 80 mg twice daily, which resulted in a comparable response in both groups.

In controlled trials, the antihypertensive effect of once-daily valsartan 80 mg was similar to that of once-daily enalapril 20 mg or once-daily lisinopril 10 mg.

There was essentially no change in heart rate in valsartan-treated patients in controlled trials.

Pediatric Hypertension

The antihypertensive effects of Diovan were evaluated in two randomized, double-blind clinical studies.

In a clinical study involving 261 hypertensive pediatric patients 6 to 16 years of age, patients who weighed < 35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥ 35 kg received 20, 80, and 160 mg of valsartan daily (low, medium and high doses). Renal and urinary disorders, and essential hypertension with or without obesity were the most common underlying causes of hypertension in children enrolled in this study. At the end of 2 weeks, valsartan reduced both systolic and diastolic blood pressure in a dose-dependent manner. Overall, the three dose levels of valsartan (low, medium and high) significantly reduced systolic blood pressure by -8, -10, -12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, systolic blood pressure at trough was -4 and -7 mm Hg lower than patients who received the placebo treatment. In patients receiving the low dose of valsartan, systolic blood pressure at trough was similar to that of patients who received the placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups

In a clinical study involving 90 hypertensive pediatric patients 1 to 5 years of age with a similar study design, there was some evidence of effectiveness, but safety findings for which a relationship to treatment could not be excluded mitigate against recommending use in this age group. *[see Adverse Reactions (6.1)]*.

14.2 Heart Failure

The Valsartan Heart Failure Trial (Val-HeFT) was a multinational, double-blind study in which 5,010 patients with NYHA class II (62%) to IV (2%) heart failure and LVEF <40%, on baseline therapy chosen by their physicians, were randomized to placebo or valsartan (titrated from 40 mg twice daily to the highest tolerated dose or 160 mg twice daily) and followed for a mean of about 2 years. Although Val-HeFT's primary goal was to examine the effect of valsartan when added to an ACE inhibitor, about 7% were not receiving an ACE inhibitor. Other background therapy included diuretics (86%), digoxin (67%), and beta-blockers (36%). The population studied was 80% male, 46% 65 years or older and 89% Caucasian. At the end of the trial, patients in the valsartan group had a blood pressure that was 4 mmHg systolic and 2 mmHg diastolic lower than the placebo group. There were two primary end points, both assessed as time to first event: all-cause mortality and heart failure morbidity, the latter defined as all-cause mortality, sudden death with resuscitation, hospitalization for heart failure, and the need for intravenous inotropic or vasodilatory drugs for at least 4 hours. These results are summarized in the table below.

	Placebo (N=2,499)	Valsartan (N=2,511)	Hazard Ratio (95% CI*)	Nominal p-value
All-cause mortality	484 (19.4%)	495 (19.7%)	1.02 (0.90-1.15)	0.8
HF morbidity	801 (32.1%)	723 (28.8%)	0.87 (0.79-0.97)	0.009

* CI = Confidence Interval

Although the overall morbidity result favored valsartan, this result was largely driven by the 7% of patients not receiving an ACE inhibitor, as shown in the following table.

	Without ACE Inhibitor		With ACE Inhibitor	
	Placebo (N=181)	Valsartan (N=185)	Placebo (N=2,318)	Valsartan (N=2,326)
Events (%)	77 (42.5%)	46 (24.9%)	724 (31.2%)	677 (29.1%)
Hazard ratio (95% CI)	0.51 (0.35, 0.73)		0.92 (0.82, 1.02)	
p-value	0.0002		0.0965	

The modest favorable trend in the group receiving an ACE inhibitor was largely driven by the patients receiving less than the recommended dose of ACE inhibitor. Thus, there is little evidence of further clinical benefit when valsartan is added to an adequate dose of ACE inhibitor.

Secondary end points in the subgroup not receiving ACE inhibitors were as follows.

	Placebo (N=181)	Valsartan (N=185)	Hazard Ratio (95% CI)
Components of HF morbidity			
All-cause mortality	49 (27.1%)	32 (17.3%)	0.59 (0.37, 0.91)
Sudden death with resuscitation	2 (1.1%)	1 (0.5%)	0.47 (0.04, 5.20)
CHF therapy	1 (0.6%)	0 (0.0%)	–
CHF hospitalization	48 (26.5%)	24 (13.0%)	0.43 (0.27, 0.71)
Cardiovascular mortality	40 (22.1%)	29 (15.7%)	0.65 (0.40, 1.05)
Non-fatal morbidity	49 (27.1%)	24 (13.0%)	0.42 (0.26, 0.69)

In patients not receiving an ACE inhibitor, valsartan-treated patients had an increase in ejection fraction and reduction in left ventricular internal diastolic diameter (LVIDD).

Effects were generally consistent across subgroups defined by age and gender for the population of patients not receiving an ACE inhibitor. The number of black patients was small and does not permit a meaningful assessment in this subset of patients.

14.3 Post-Myocardial Infarction

The VALsartan In Acute myocardial iNfarcTion trial (VALIANT) was a randomized, controlled, multinational, double-blind study in 14,703 patients with acute myocardial infarction and either heart failure (signs, symptoms or radiological evidence) or left ventricular systolic dysfunction (ejection fraction ≤40% by radionuclide ventriculography or ≤35% by echocardiography or ventricular contrast angiography). Patients were randomized within 12 hours to 10 days after the onset of myocardial infarction symptoms to one of three treatment groups: valsartan (titrated from 20 or 40 mg twice daily to the highest tolerated dose up to a maximum of 160 mg twice daily), the ACE inhibitor, captopril (titrated from 6.25 mg three times daily to the highest tolerated dose up to a maximum of 50 mg three times daily), or the combination of valsartan plus captopril. In the combination group, the dose of valsartan was titrated from 20 mg twice daily to the highest tolerated dose up to a maximum of 80 mg twice daily; the dose of captopril was the same as for monotherapy. The population studied was 69% male, 94% Caucasian, and 53% were 65 years of age or older. Baseline therapy included aspirin (91%), beta-blockers (70%), ACE inhibitors (40%), thrombolytics (35%) and statins (34%). The mean treatment duration was two years. The mean daily dose of Diovan in the monotherapy group was 217 mg.

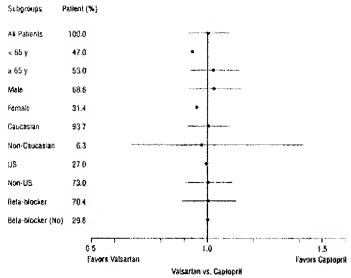
The primary endpoint was time to all-cause mortality. Secondary endpoints included (1) time to cardiovascular (CV) mortality, and (2) time to the first event of cardiovascular mortality, reinfarction, or hospitalization for heart failure. The results are summarized in the table below:

	Valsartan vs. Captopril (N=4,909) (N=4,909)			Valsartan + Captopril vs. Captopril (N=4,885) (N=4,909)		
	No. of Deaths Valsartan/Captopril	Hazard Ratio CI	p-value	No. of Deaths Comb/Captopril	Hazard Ratio CI	p-value
All-cause mortality	979 (19.9%) /958 (19.5%)	1.001 (0.902, 1.111)	0.98	941 (19.3%) /958 (19.5%)	0.984 (0.886, 1.093)	0.73
CV mortality	827 (16.8%) /830 (16.9%)	0.976 (0.875, 1.090)				
CV mortality, hospitalization for HF, and recurrent non-fatal MI	1,529 (31.1%) /1,567 (31.9%)	0.955 (0.881, 1.035)				

There was no difference in overall mortality among the three treatment groups. There was thus no evidence that combining the ACE inhibitor captopril and the angiotensin II blocker valsartan was of value.

The data were assessed to see whether the effectiveness of valsartan could be demonstrated by showing in a non-inferiority analysis that it preserved a fraction of the effect of captopril, a drug with a demonstrated survival effect in this setting. A conservative estimate of the effect of captopril (based on a pooled analysis of 3 post-infarction studies of captopril and 2 other ACE inhibitors) was a 14-16% reduction in mortality compared to placebo. Valsartan would be considered effective if it preserved a meaningful fraction of that effect and unequivocally preserved some of that effect. As shown in the table, the upper bound of the CI for the hazard ratio (valsartan/captopril) for overall or CV mortality is 1.09-1.11, a difference of about 9-11%, thus making it unlikely that valsartan has less than about half of the estimated effect of captopril and clearly demonstrating an effect of valsartan. The other secondary endpoints were consistent with this conclusion.

Effects on Mortality Amongst Subgroups in VALIANT



There were no clear differences in all-cause mortality based on age, gender, race, or baseline therapies, as shown in the figure above.

16 HOW SUPPLIED/STORAGE AND HANDLING

Diovan (valsartan) is available as tablets containing valsartan 40 mg, 80 mg, 160 mg, or 320 mg. All strengths are packaged in bottles and unit dose blister packages (10 strips of 10 tablets) as described below.

40 mg tablets are scored on one side and ovaloid with bevelled edges. 80 mg, 160 mg, and 320 mg tablets are unscored and almond-shaped with bevelled edges.

Tablet	Color	Deboss		NDC 0078-XXXX-XX		
		Side 1	Side 2	Bottle of		Blister
				30	90	Packages of 100
40 mg	Yellow	NVR	DO	0423-15	–	0423-06
80 mg	Pale red	NVR	DV	–	0358-34	0358-06
160 mg	Grey-orange	NVR	DX	–	0359-34	0359-06
320 mg	Dark grey-violet	NVR	DXL	–	0360-34	0360-06

Store at 25°C (77°F); excursions permitted to 15-30°C (59 - 86°F) [see USP Controlled Room Temperature].

Protect from moisture.

Dispense in tight container (USP).

17 PATIENT COUNSELING INFORMATION

17.1 Information for Patients

Pregnancy: Female patients of childbearing age should be told that use of drugs like Diovan that act on the renin-angiotensin system during pregnancy can cause serious problems in the fetus and infant including: low blood pressure, poor development of skull bones, kidney failure and death. Women using Diovan who become pregnant should notify their physician as soon as possible.

DIOVAN (DYE'-o-van)
(valsartan) Tablets

Read the Patient Information that comes with DIOVAN before you take it and each time you get a refill. There may be new information. This leaflet does not take the place of talking with your doctor about your medical condition or treatment. If you have any questions about DIOVAN, ask your doctor or pharmacist.

What is the most important information I should know about DIOVAN?

Taking DIOVAN during pregnancy can cause injury and even death to your unborn baby. If you get pregnant, stop taking DIOVAN and call your doctor right away. Talk to your doctor about other ways to lower your blood pressure if you plan to become pregnant.

What is DIOVAN?

DIOVAN is a prescription medicine called an angiotensin receptor blocker (ARB). It is used in adults to:

- lower high blood pressure (hypertension) in adults and children, 6 to 16 years of age.
- treat heart failure in adults. In these patients, DIOVAN may lower the need for hospitalization that happens from heart failure.
- improve the chance of living longer after a heart attack (myocardial infarction) in adults.

DIOVAN is not for children under 6 years of age or children with certain kidney problems.

High Blood Pressure (Hypertension). Blood pressure is the force in your blood vessels when your heart beats and when your heart rests. You have high blood pressure when the force is too much. DIOVAN can help your blood vessels relax so your blood pressure is lower.

High blood pressure makes the heart work harder to pump blood throughout the body and causes damage to the blood vessels. If high blood pressure is not treated, it can lead to stroke, heart attack, heart failure, kidney failure and vision problems.

Heart Failure occurs when the heart is weak and cannot pump enough blood to your lungs and the rest of your body. Just walking or moving can make you short of breath, so you may have to rest a lot.

Heart Attack (Myocardial Infarction): A heart attack is caused by a blocked artery that results in damage to the heart muscle.

What should I tell my doctor before taking DIOVAN?

Tell your doctor about all your medical conditions including whether you:

- have any allergies. See the end of this leaflet for a complete list of ingredients in DIOVAN.
- have a heart condition
- have liver problems
- have kidney problems
- **are pregnant or planning to become pregnant.** See "What is the most important information I should know about DIOVAN?"
- are breast-feeding. It is not known if DIOVAN passes into your breast milk. You and your doctor should decide if you will take DIOVAN or breast-feed, but not both. Talk with your doctor about the best way to feed your baby if you take DIOVAN.

Tell your doctor about all the medicines you take including prescription and nonprescription medicines, vitamins and herbal supplements. Especially tell your doctor if you take:

- other medicines for high blood pressure or a heart problem
- water pills (also called "diuretics")
- potassium supplements
- a salt substitute

Know the medicines you take. Keep a list of your medicines with you to show to your doctor and pharmacist when a new medicine is prescribed. Talk to your doctor or pharmacist before you start taking any new medicine. Your doctor or pharmacist will know what medicines are safe to take together.

How should I take DIOVAN?

- Take DIOVAN exactly as prescribed by your doctor.
- For treatment of high blood pressure, take DIOVAN one time each day, at the same time each day.
- If your child cannot swallow tablets, or if tablets are not available in the prescribed strength, your pharmacist will mix DIOVAN as a liquid suspension for your child. If your child switches between taking the tablet and the suspension, your doctor will adjust the dose as needed. Shake the bottle of suspension well for at least 10 seconds before pouring the dose of medicine to give to your child.
- For adult patients with heart failure or who have had a heart attack, take DIOVAN two times each day, at the same time each day. Your doctor may start you on a low dose of DIOVAN and may increase the dose during your treatment.
- DIOVAN can be taken with or without food.
- If you miss a dose, take it as soon as you remember. If it is close to your next dose, do not take the missed dose. Take the next dose at your regular time.
- If you take too much DIOVAN, call your doctor or Poison Control Center, or go to the nearest hospital emergency room.

What are the possible side effects of DIOVAN?

DIOVAN may cause the following serious side effects:

Injury or death to an unborn baby. See "What is the most important information I should know about DIOVAN?"

Low Blood Pressure (Hypotension). Low blood pressure is most likely to happen if you also take water pills, are on a low-salt diet, get dialysis treatments, have heart problems, or get sick with vomiting or diarrhea. Lie down, if you feel faint or dizzy. Call your doctor right away.

Kidney problems. Kidney problems may get worse in people that already have kidney disease. Some people will have changes on blood tests for kidney function and may need a lower dose of DIOVAN. Call your doctor if you get swelling in your feet, ankles, or hands, or unexplained weight gain. If you have heart failure, your doctor should check your kidney function before prescribing DIOVAN.

The most common side effects of DIOVAN used to treat people with high blood pressure include:

- headache
- dizziness
- flu symptoms
- tiredness
- stomach (abdominal) pain

Side effects were generally mild and brief. They generally have not caused patients to stop taking DIOVAN.

The most common side effects of DIOVAN used to treat people with heart failure include:

- dizziness
- low blood pressure
- diarrhea
- Joint and back pain
- tiredness
- high blood potassium

Common side effects of DIOVAN used to treat people after a heart attack which caused them to stop taking the drug include:

- low blood pressure
- cough

- high blood creatinine (decreased kidney function)
- rash

Tell your doctor if you get any side effect that bothers you or that does not go away.

These are not all the possible side effects of DIOVAN. For a complete list, ask your doctor or pharmacist.

How do I store DIOVAN?

- Store DIOVAN tablets at room temperature between 59o to 86oF (15°C - 30°C).
- Keep DIOVAN tablets in a closed container in a dry place.
- Store bottles of DIOVAN suspension at room temperature less than 86°F (30°C) for up to 30 days, or refrigerate between 35°F - 46°F (2°C - 8°C) for up to 75 days.
- Keep DIOVAN and all medicines out of the reach of children.

General Information about DIOVAN

Medicines are sometimes prescribed for conditions that are not mentioned in patient information leaflets. Do not use DIOVAN for a condition for which it was not prescribed. Do not give DIOVAN to other people, even if they have the same symptoms you have. It may harm them.

This leaflet summarizes the most important information about DIOVAN. If you would like more information, talk with your doctor. You can ask your doctor or pharmacist for information about DIOVAN that is written for health professionals.

For more information about DIOVAN, ask your pharmacist or doctor, visit www.DIOVAN.com on the Internet, or call 1-866-404-6361.

What are the Ingredients in DIOVAN?

Active ingredient: valsartan

Inactive ingredients: colloidal silicon dioxide, crospovidone, hydroxypropyl methylcellulose, iron oxides (yellow, black and/or red), magnesium stearate, microcrystalline cellulose, polyethylene glycol 8000, and titanium dioxide

REV: DECEMBER 2008 T2008-108/T2007-110

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Distributed by:

Novartis Pharmaceuticals Corp.
East Hanover, NJ 07936